=> file reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 16:32:16 ON 29 APR 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 APR 2005 HIGHEST RN 849459-72-9
DICTIONARY FILE UPDATES: 28 APR 2005 HIGHEST RN 849459-72-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

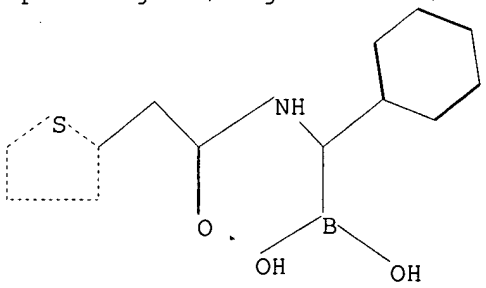
Please note that search-term pricing does apply when conducting SmartSELECT searches.

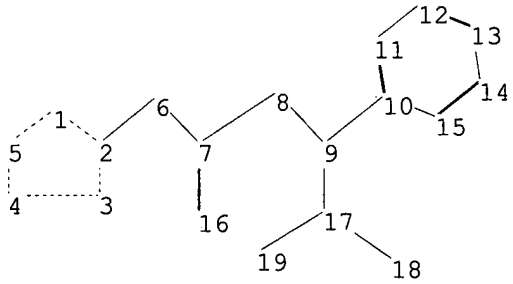
****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10731738.str





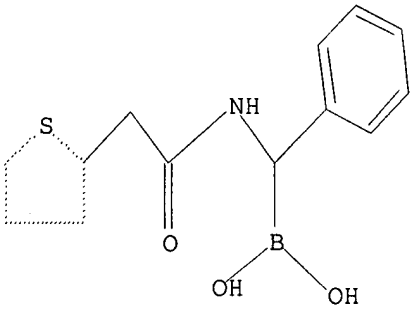
chain nodes :
6 7 8 9 16 17 18 19
ring nodes :
1 2 3 4 5 10 11 12 13 14 15
chain bonds :
2-6 6-7 7-8 7-16 8-9 9-10 9-17 17-18 17-19
ring bonds :
1-2 1-5 2-3 3-4 4-5 10-11 10-15 11-12 12-13 13-14 14-15
exact/norm bonds :
1-2 1-5 2-3 3-4 4-5 7-8 7-16 8-9
exact bonds :
2-6 6-7 9-10 9-17 17-18 17-19

normalized bonds :
10-11 10-15 11-12 12-13 13-14 14-15

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:CLASS 17:CLASS 18:CLASS
19:CLASS

L1 STRUCTURE UPLOADED

=> d
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 16:32:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 0 TO ITERATE

100.0% PROCESSED 0 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 0 TO 0
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 16:32:34 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 15 TO ITERATE

100.0% PROCESSED 15 ITERATIONS 4 ANSWERS
SEARCH TIME: 00.00.01

L3 4 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 161.33 161.54

FILE 'CAPLUS' ENTERED AT 16:32:37 ON 29 APR 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 29 Apr 2005 VOL 142 ISS 19
FILE LAST UPDATED: 28 Apr 2005 (20050428/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 3 L3

=> d ibib abs hitstr tot

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:897312 CAPLUS
DOCUMENT NUMBER: 140:89783
TITLE: Thermodynamic Cycle Analysis and Inhibitor Design against Beta-Lactamase
AUTHOR(S): Roth, Tomer A.; Minasov, George; Morandi, Stefania; Prati, Fabio; Shoichet, Brian K.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, 94143-2240, USA
SOURCE: Biochemistry (2003), 42(49), 14483-14491
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:89783

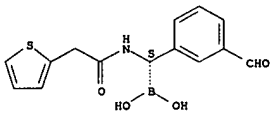
AB β-Lactamases are the most widespread resistance mechanism to β-lactam antibiotics, such as the penicillins and cephalosporins. Transition-state analogs that bind to the enzymes with nanomolar affinities have been introduced in an effort to reverse the resistance conferred by these enzymes. To understand the origins of this affinity, and to guide design of future inhibitors, double-mutant thermodn. cycle expts. were undertaken. An unexpected hydrogen bond between the nonconserved Asn289 and a key inhibitor carboxylate was observed in the X-ray crystal structure of a 1 nM inhibitor (compound 1) in complex with AmpC β-lactamase. To investigate the energy of this hydrogen bond, the mutant enzyme N289A was made, as was an analog of 1 that lacked the carboxylate (compound 2). The differential affinity of the four different protein and analog complexes indicates that the carboxylate-amide hydrogen bond contributes 1.7 kcal/mol to overall binding affinity. Synthesis of an analog of 1 where the carboxylate was replaced with an aldehyde led to an inhibitor that lost all this hydrogen bond energy, consistent with the importance of the ionic nature of this hydrogen bond. To investigate the structural bases of these energies, X-ray crystal structures of N289A/1 and N289A/2 were determined to 1.49 and 1.39 Å, resp. These structures suggest that no significant rearrangement occurs in the mutant vs. the wild-type complexes with both compds. The mutant enzymes L119A and L293A were made to investigate the interaction between a Ph ring in 1 and these residues. Whereas deletion of the Ph itself diminishes affinity by 5-fold, the double-mutant cycles suggest that this energy does not come through interaction with the leucines, despite the close contact in the structure. The energies of these interactions provide key information for the design of improved inhibitors against β-lactamases. The high magnitude of the ion-dipole interaction between Asn289 and the carboxylate of 1 is consistent with the idea that ionic interactions can provide significant net affinity in inhibitor complexes.

IT **643767-35-5D**, complexes with AmpC β-lactamase
643767-36-6D, complexes with AmpC β-lactamase
RL: PRP (Properties)
(thermodn. cycle and mutational anal. address hydrogen bond interaction between Asn289 residue of AmpC β-lactamase and carboxylate group of inhibitor mol.)

RN 643767-35-5 CAPLUS
CN Boronic acid, [(S)-(3-formylphenyl)[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

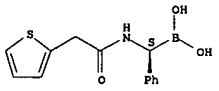
L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)

Absolute stereochemistry.



RN 643767-36-6 CAPLUS
CN Boronic acid, [(S)-phenyl[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:478576 CAPLUS
DOCUMENT NUMBER: 139:175717
TITLE: Recognition and resistance in TEM β-lactamase
AUTHOR(S): Wang, Xiaojun; Minasov, George; Blazquez, Jesus; Caselli, Emilia; Prati, Fabio; Shoichet, Brian K.
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of California San Francisco, San Francisco, CA, 94143, USA
SOURCE: Biochemistry (2003), 42(28), 8434-8444
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

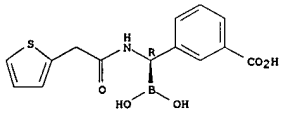
AB Developing antimicrobials that are less likely to engender resistance has become an important design criterion as more and more drugs fall victim to resistance mutations. One hypothesis is that the more closely an inhibitor resembles a substrate, the more difficult it will be to develop resistant mutations that can at once disfavor the inhibitor and still recognize the substrate. To investigate this hypothesis, 10 transition-state analogs, of greater or lesser similarity to substrates, were tested for inhibition of TEM-1 β-lactamase, the most widespread resistance enzyme to penicillin antibiotics. The inhibitors were also tested against four characteristic mutant enzymes: TEM-30, TEM-32, TEM-52, and TEM-64. The inhibitor most similar to the substrate, compound 10, was the most potent inhibitor of the WT enzyme, with a Ki value of 64 nM. Conversely, compound 10 was the most susceptible to the TEM-30 (R244S) mutant, for which inhibition dropped by over 100-fold. The other inhibitors were relatively impervious to the TEM-30 mutant enzyme. To understand recognition and resistance to these transition-state analogs, the structures of four of these inhibitors in complex with TEM-1 were determined by x-ray crystallog. These structures suggest a structural basis for distinguishing inhibitors that mimic the acylation transition state and those that mimic the deacylation transition state; they also suggest how TEM-30 reduces the affinity of compound 10. In cell culture, this inhibitor reversed the resistance of bacteria to ampicillin, reducing min. inhibitory concns. of this penicillin by between 4- and 64-fold, depending on the strain of bacteria. Notwithstanding this activity, the resistance of TEM-30, which is already extant in the clinic, suggests that there can be resistance liabilities with substrate-based design.

IT **497258-67-0D**, complexes with TEM-1 β-lactamase
RL: PRP (Properties)
(crystal structure of TEM-1 β-lactamase-transition state analog complexes)

RN 497258-67-0 CAPLUS
CN Benzoic acid, 3-[(R)-borono[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

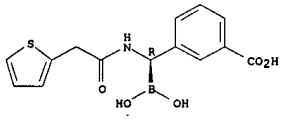
L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



IT **497258-67-0**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transition state analog recognition and inhibition by TEM β-lactamase mutants in relation to antibiotic resistance)

RN 497258-67-0 CAPLUS
CN Benzoic acid, 3-[(R)-borono[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:977460 CAPLUS
DOCUMENT NUMBER: 138:165634
TITLE: Nanomolar Inhibitors of AmpC β-Lactamase
AUTHOR(S): Morandi, Federica; Caselli, Emilia; Morandi, Stefania; Focia, Pamela J.; Blazquez, Jesus; Shoichet, Brian K.; Prati, Fabio
CORPORATE SOURCE: Department of Pharmaceutical Chemistry, University of California, San Francisco, CA, 94143, USA
SOURCE: Journal of the American Chemical Society (2003), 125(3), 685-695
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:165634

Instant Applicant

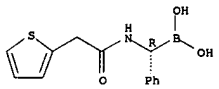
AB β-Lactamases are the most widespread resistance mechanism to β-lactam antibiotics, such as the penicillins and the cephalosporins. In an effort to combat these enzymes, a combination of stereoselective organic synthesis, enzymol., microbiol., and X-ray crystallog. was used to design and evaluate new carboxyphenyl-glycylboronic acid transition-state analog inhibitors of the class C β-lactamase AmpC. The new compds. improve inhibition by over 2 orders of magnitude compared to analogous glycylboronic acids, with Ki values as low as 1 nM. On the basis of the differential binding of different analogs, the introduced carboxylate alone contributes about 2.1 kcal/mol in affinity. This carboxylate corresponds to the ubiquitous C3(4)' carboxylate of β-lactams, and this energy represents the first thermodn. measurement of the importance of this group in mol. recognition by class C β-lactamases. The structures of AmpC in complex with two of these inhibitors were determined by X-ray crystallog. at 1.72 and 1.83 Å resolution These structures suggest a structural basis for the high affinity of the new compds. and provide templates for further design. The highest affinity inhibitor was 5 orders of magnitude more selective for AmpC than for characteristic serine proteases, such as chymotrypsin. This inhibitor reversed the resistance of clin. pathogens to the third generation cephalosporin ceftazidime; it may serve as a lead compound for drug discovery to combat bacterial resistance to β-lactam antibiotics.

IT **497258-67-0D**, complexes with AmpC β-lactamase
497258-70-5D, complexes with AmpC β-lactamase
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(carboxyphenyl-glycylboronic acid transition-state analog inhibitors can inhibit AmpC β-lactamase)

RN 497258-67-0 CAPLUS
CN Benzoic acid, 3-[(R)-borono[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

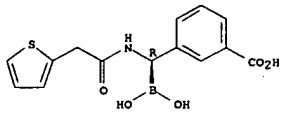
Absolute stereochemistry.

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



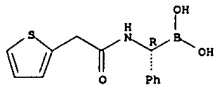
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2005 ACS on STN (Continued)



RN 497258-70-5 CAPLUS
CN Boronic acid, [(R)-phenyl[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

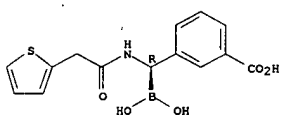
Absolute stereochemistry. Rotation (-).



IT **497258-67-0P 497258-70-5P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(carboxyphenyl-glycylboronic acid transition-state analog inhibitors can inhibit AmpC β-lactamase)

RN 497258-67-0 CAPLUS
CN Benzoic acid, 3-[(R)-borono[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 497258-70-5 CAPLUS
CN Boronic acid, [(R)-phenyl[(2-thienylacetyl)amino]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).